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Adjunct Duties for Karyopherins: Regulating Septin Sumoylation

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Karyopherins are shuttling transport receptors regulated by the small GTPase Ran, which move cargo between the nucleus and cytoplasm by passing through the nuclear pore complexes. A recent paper in *Journal of Cell Biology* (Makhnevych et al., 2007) highlights an additional role for karyopherins during mitosis, in regulating the sumoylation status of the septin rings.

Septins are long filamentous GTPases that assemble as a ring structure at the yeast bud neck in the G1 phase of the cell cycle. As the bud grows this ring extends through the bud neck, forming an hourglass-shaped structure and appears as a double ring in the mother and daughter cell. The ring then divides during cytokinesis and is later disassembled (Longtine and Bi, 2003). The first major identified SUMO-1 targets in budding yeast were the members of the septin ring (Cdc3, Cdc11, and Shs1). Moreover, the septins were shown to become sumoylated during mitosis prior to anaphase and desumoylated at cytokinesis (Johnson and Blobel, 1999). Now Wozniak and colleagues have provided a mechanistic insight into how the cyclic processes of septin sumoylation and subsequent desumoylation are triggered during the course of the cell cycle (Makhnevych et al., 2007).

Sumoylation of the cortical septins is carried out by the RING-like SUMO E3 ligase Siz1 (Johnson and Gupta, 2001), but during interphase Siz1 is located inside the nucleus. How can Siz1 gain access to the cortically located septins? The recent study by Wozniak and colleagues has unraveled that during interphase the karyopherin Kap95 (an importin) is responsible to transport Siz1 into the nucleus (Makhnevych et al., 2007). However, during mitosis before the onset of anaphase, Siz1 becomes phosphorylated (Johnson and Gupta, 2001) and in turn is exported from the nucleus by the karyopherin Kap142/Msn5 (an exportin). In the cytoplasm, Siz1 is targeted to the bud neck to promote septin sumoylation. Thus, cell-cycle-dependent septin sumoylation requires regulated nucleocytoplasmic transport and the coordinated action of an importin and exportin that move the SUMO E3 ligase Siz1from the cytoplasm to the nucleus and back.

How are the septins desumoylated? Septin desumoylation occurs at cytokinesis and is carried out by Ulp1, a desumoylating enzyme that is located at the nuclear pore complex (NPC) (Li and Hochstrasser, 2000; Takahashi et al., 2000). The bulk of the cellular Ulp1 is anchored to the NPC via its regulatory N-domain that exhibits two distinct binding sites for karyopherins, the Kap95/Kap60 complex and Kap121, respectively (Panse et al., 2003). Kap95/Kap60 recognizes the classical nuclear localization sequence (NLS) present in a large number of nuclear cargo proteins while Kap121 is involved in the nuclear import of cargo proteins with a different type of NLS (Suntharalingam and Wente, 2003). However, the nature of the interaction between Ulp1 and the karyopherin transport receptors was found to be of a non-cargo-type since it was found to be insensitive to RanGTP (Panse et al., 2003). Since Ulp1 is tethered to the NPC via its interaction with the Kap121 and Kap60/Kap95, how can Ulp1 reach the bud neck during cytokinesis to remove SUMO from the septins? The work by Makhnevych et al. (2007) demonstrates that Ulp1 is transiently released from the NPCs at mitosis thereby facilitating desumoylation of the septins during cytokinesis. Ulp1 release is prompted by change in its association specifically with Kap121. Together, this work throws light on the conventional (transport) and adjunct roles (tethering and regulated release) played by the karyopherins Kap95, Kap121, and Kap142/Msn5 in regulating transient septin sumoylation.

Prior to this study the functional significance of Ulp1 NPC anchoring remained unclear. This new study has provided insight into how such anchoring and controlled release of the desumoylating enzyme Ulp1 can be exploited to regulate a cellular pathway that requires cell-cycle-dependent sumoylation. Due to these findings one can hypothesize that the triggered release of Ulp1 from NPCs may be also exploited for other SUMO-carrying substrate proteins that require cell-cycle-dependent SUMO-modification. In yeast, proteomic approaches have uncovered many sumoylated nuclear proteins that affect diverse cellular processes such as DNA replication and repair, transcription, or chromatin remodeling (Johnson, 2004). Thus, it is possible that the timed release of Ulp1 from its specific NPC anchors affects the sumoylation status of a number of these proteins. This speculation is in line with a previous observation that the deletion of specific Kap binding sites in Ulp1 resulted in different patterns of sumoylated proteins (Li and Hochstrasser, 2003). Unraveling these proteins could help to further understand the role of Kap121- and Kap95/Kap60-mediated tethering to the NPC. What remains to be shown

is the mechanism by which Ulp1 can be released from the NPCs during septin desumoylation, but alteration of the NPC conformation during cytokinesis could be one of the means to trigger this process (Makhnevych et al., 2003).

In summary, this work has shed light on the dynamic interplay of karyopherins in regulating septin sumoylation at the bud neck, which also has implications for the regulation of other sumoylated proteins involved in diverse processes.

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